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A simple one-pot synthesis of 3-alkoxy-3-cyanocarboxylic acids: a rapid entry to new GABA derivatives

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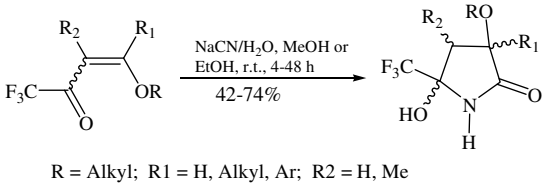
Abstract—A simple one-pot procedure to obtain a series of new 3-alkoxy-3-cyanocarboxylic acids from the reaction of 4-alkoxy-1,1,1-trichloro-but-3-en-2-ones with sodium cyanide is described.

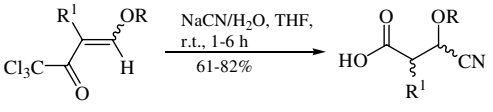
β-Cyanocarboxylic acids are of great interest for a variety of applications due to the versatility of these two functional groups as precursors of many other organic functions. For example, the cyano group can easily be converted to carboxylic acid,[1] amides,[2] primary amines,[3] amidines,[4] and heterocycles such as tetrazoles,[5,6] imidazoles,[7] and lactams.[8] The carboxyl group can be converted into esters, nitriles,[9] amides,[8,10] acyl ureas,[8] and oxazolines,[10] just to mention a few. However, one of the most significant applications of 3-cyanocarboxylic acids are as precursors of GABA derivatives,[3,11] succinimides,[12] and lactams.[13] Cyanocarboxylic acids have been prepared through the selective hydrolysis of aliphatic dinitriles carried out by enzymes,[1,13,14] or by a multi-step synthesis.[3,11,15]

In a recent work, we reported the synthesis of a new series of 3-alkoxy-5-hydroxy-5-trifluoromethyl-pyrrolidin-2-ones from the reaction of 4-alkoxy-1,1,1-trifluoroalk-3-en-2-ones with sodium cyanide in hydro-alcoholic solution, according to Scheme 1.[16] However, when the same reaction was performed on the 4-alkoxy-1,1,1-trichloro-alk-3-en-2-ones, only 3-alkoxy-3-cyanopropanoic acids **2** (Scheme 2) were obtained, instead of the expected 3-alkoxy-5-hydroxy-5-trichloromethyl-pyrrolidin-2-ones. The elimination of the trichloromethyl group, in basic medium, has been reported previously.[17] However, to the best of our knowledge, no description of the synthesis of 3-alkoxy-3-cyanopropanoic acids has been reported.



R = Alkyl; R1 = H, Alkyl, Ar; R2 = H, Me

Scheme 1.



1a-h **2a-h**

1, 2	R	R1
a	Et	H
b	Et	Me
c	-(CH2)2-	
d	-(CH2)3-	

1, 2	R	R1
e	*iso*-Pr	H
f	*iso*-Pr	Me
g	*sec*-Bu	H
h	*sec*-Bu	Me

Scheme 2.

Thus, considering the synthetic versatility of 3-cyanopropanoic acids as precursors of a wide range of

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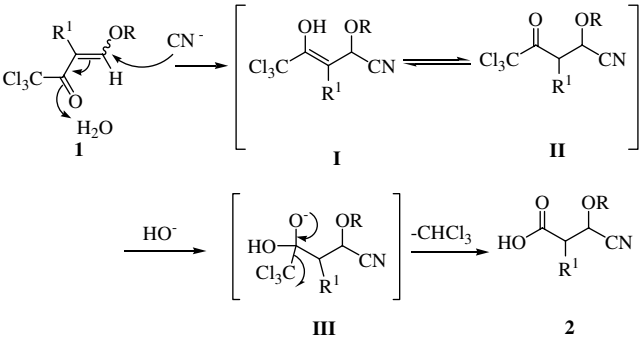
interesting aliphatic and heterocyclic compounds we wish to present a very simple one-pot procedure to obtain a series of 3-alkoxy-3-cyanopropanoic acids from the readily available 4-alkoxy-1,1,1-trichloro-alk-3-en-2-ones.[18] The synthetic versatility of these trichlorinated enones has been recently demonstrated for the preparation of 3-amino-ethylene-dihydrofuran-2-ones,[19] pyrazoles and pyrazolium chlorides,[20] furan-3-carboxylic acids and derivatives,[21] pyrazole-carboxyamide,[22] azolylmethyl-pyrimidin-2-ones,[23] and 4-trichloromethyl-2-methylsulfanyl pyrimidines.[24] The synthesis and applications of 4-alkoxy-1,1,1-trichloro-alk-3-en-2-ones have also been the subject of a recent review.[25]

Scheme 2 outlines the synthesis of 3-alkoxy-3-cyanopro panoic acids **2a**–**h** from the reaction of the enones **1a**–**h** with a solution of sodium cyanide in water and THF.[26] The reactions furnished better yields when carried out with two equivalents of sodium cyanide, at room temperature, from 1 to 6 h, according to Table 1. Compounds **1a**–**d**, were prepared according to Ref. 18 and compounds **1e**–**h** were obtained by trans-etherification of **1a** and **1b** with *iso*-propanol and *sec*-butanol, as reagents and reaction solvents, and using catalytic amounts of *p*-toluenesulfonic acid.[27] Products **2a**–**h** were isolated through two extractions: In the first, the pH is basic due to the reaction (pH ~ 10) and the solution was extracted with ethyl ether to eliminate possible unreacted starting material. In the second extraction, the pH of the water layer was lowered to about three with the addition of 1 M solution of hydrochloric acid and the solution was extracted with ethyl ether in order to recover the products **2a**–**h** in the organic phase. The organic phase was dried under magnesium sulfate, filtered, and the solvent was evaporated to render 3-alkoxy-3-cyanocarboxylic acids **2a**–**h**, in good yields and high purity (Table 1). All compounds were analyzed by ^{1}H and ^{13}C NMR, IR, and GC–MS.[28] It was observed that the cyano group of compounds **2** slowly hydrolyzes to an amide group if maintained at room temperature, probably due to the presence of the carboxylic acid group and moisture. Compounds such as **2b**, **2d**, **2f**, and **2g** have two asymmetric carbons and they were obtained as a mixture of diastereoisomers in proportions, determined by ^{1}H NMR integrals and presented in Table 1. Compounds **2c** also has two asymmetric carbons but this compound shows only a pair of enantiomers. Compounds **2h** has three asymmetric carbons and this compound presented four diastereoisomers in a proportion indicated in Table 1.

Under the reaction conditions shown in Scheme 2, 4-alkyl substituted 4-alkoxyvinyl trichloromethyl ketones failed to react probably due to the formation of an enolate corresponding to the deprotonation of the γ-carbon.[29]

The possible mechanism for the formation of 3-alkoxy-3-cyanocarboxylic acids **2** (Scheme 3) starts with the Michael addition of a cyanide ion on the β-carbon of enones **1** to form the tautomeric structures **I** and **II**, in which the carbonyl function becomes activated toward a nucleophilic attack due to the addition of the cyanide on the double bond. The nucleophilic addition of a hydroxyl group from a water molecule on the carbonyl of structure **II** affords intermediate **III**, which eliminates the CCl_3 group to furnish the 3-alkoxy-3-cyanocarboxylic acids **2** (Scheme 3).

In a second reaction, compound **1a** was converted to the 3-bromo enone derivative **3**, through a reaction with bromine in chloroform and pyridine[30] (Scheme 4). Compound **3** was reacted using the same protocol shown in Scheme 2, but the obtained product was the 1-ethoxy-

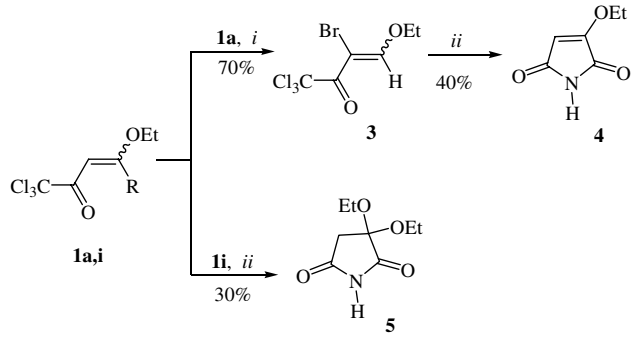


Scheme 3.

Table 1. Reaction conditions, yields, and proportion of diastereoisomers formed on the synthesis of compounds **2**

Compound	Time (h)	Proportion of diastereoisomers[a]	Yield[b] (%)	Product[c]
1a	1	[d]	72	**2a**
1b	4	2:1	70	**2b**
1c	4	[d]	61	**2c**
1d	6	3:1	66	**2d**
1e	4	[d]	79	**2e**
1f	4	3:2	78	**2f**
1g	4	3:2	78	**2g**
1h	4	3:2:1:1	82	**2h**

[a] Determined by ^{1}H NMR integrals.
[b] Yields of isolated compounds.
[c] Reaction condition: NaCN (2 equiv)/H_2O, THF, rt.
[d] Obtained as a racemic mixture.



1a: R = H
1i: R = OEt

Scheme 4. Reagents and conditions: (i) (1) Br_2, $CHCl_3$, rt, 1 h. (2) Py, 0–25 °C, 16 h. (ii) NaCN (2.0 equiv), H_2O, THF, rt, 20 h.

1*H*-pyrrole-2,5-dione (**4**) instead of the expected 3-alkoxy-2-bromo-3-cyanopropanoic acid. In addition, 4, 4-diethoxy-1,1,1-trichloro-but-3-en-2-one[31] (**1i**) was reacted with sodium cyanide (Scheme 4) using the same protocol shown in Scheme 2. This reaction furnished the cyclic 3,3-diethoxypyrrolidin-2,5-dione (**5**) instead of the aliphatic 3,3-diethoxy-3-cyanopropanoic acid.

According to Stevens et al.,[32] the formation of the cyclic imides **4** and **5** possibly resulted from a Michael addition of the cyanide ion on the β-carbon of enones **3** and **1i** forming the 3-bromo-5,5,5-trichloro-2-ethoxy-4-oxopentanenitrile and the 5,5,5-trichloro-2,2-diethoxy-4-oxopentanenitrile intermediates, respectively, which were not isolated. Subsequent hydrolysis of the cyano group to an amide followed by an intramolecular attack of the amide nitrogen to the α-trichloro-carbonyl and subsequent elimination of the CCl_3 group furnishing compounds **4** and **5**.

In conclusion, this study showed a simple and efficient one-pot procedure to obtain a series of new 3-alkoxy-3-cyanocarboxylic acids, directly from the readily available 4-alkoxy-1,1,1-trichloro-but-3-en-2-ones. The 3-cyanocarboxylic acids obtained in this study can be considered as potential intermediates of a new class of GABA derivatives that can be synthesized through a selective reduction of the cyano group to an amine group.

Acknowledgments

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26. *General procedure for the synthesis of 3-alkoxy-3-cyano carboxylic acids* **2**: To a solution of the enones **1** (5.0 mmol) in THF (3.0 mL) a solution of sodium cyanide (0.24 g, 5.0 mmol) in water (3.0 mL) was added, under stirring, at room temperature. The reaction mixture was stirred for 30 min and a new addition of a solution of sodium cyanide (0.24 g, 5.0 mmol) in water (3 mL) was added and the stirring was continued for 1–6 h, at room temperature. The products **2a**–**h** were isolated through two extractions; in the first, the pH is basic from the reaction (pH ~10) and the solution was extracted with ethyl ether (2 × 20 mL) to eliminate possible unreacted starting material. In the second extraction, the pH was lowered to about three with the addition of 1 M solution of hydrochloric acid and the solution was extracted with ethyl ether (2 × 20 mL) to recover the products **2a**–**h** in the organic phase. The organic phase was dried under magnesium sulfate, filtered, and the solvent was evaporated to render

3-alkoxy-3-cyanocarboxylic acids **2a**–**h**, as oils, in good yields, and high purity.

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28. Following are ^{1}H and ^{13}C NMR, IR, and GC–MS spectral data of representative compounds: Compound **2a**: δ_H (200 MHz, $CDCl_3$): 1.26 (t, 3H, $J = 6.8$, $OCCH_3$), 2.93 (d, 2H, $J_{H2–H3} = 8.0$, H-2), 3.58–3.85 (m, 2H, OCH_2–), 4.55 (t, $J_{H3–H2} = 8.0$, H-3), 9.00 (s, 1H, OH). δ_C (100 MHz, $CDCl_3$): 14.5 ($OCCH_3$), 38.2 (C-2), 64.2 (OCH_2–), 66.7 (C-3), 117.3 (CN), 173.6 (CO). GC–MS (EI, 70 eV) *m*/*z* (%): 142 (M^+−H, 1), 114 (5), 98 (43), 87 (41), 71 (19), 54 (100). IR (neat) 2500–3500, 2250, 1714.
Compound **2b** (major compound): δ_H (200 MHz, $CDCl_3$): 1.25 (t, 3H, $J = 6.0$, $OCCH_3$), 1.40 (d, 3H, $J_{CH3–H2} = 6.0$, CH_3), 2.88–3.03 (m, 1H, H-2), 3.49–3.65 (m, 2H, OCH_2–), 4.42 (d, 1H, $J_{H3–H2} = 8.0$, H-3), 9.69 (s, 1H, OH). δ_C (100 MHz, $CDCl_3$): 12.8 ($OCCH_3$), 14.5 (–CH_3), 43.1 (C-2), 66.8 (OCH_2–), 70.2 (C-3), 116.7 (CN), 177.4 (CO). GC–MS (EI, 70 eV) *m*/*z* (%): 157 (M^+, 1), 127 (6), 112 (25), 101 (30), 74 (100), 68 (72), 56 (80). IR (neat) 2500–3500, 2257, 1717.
Compound **2c**: δ_H (200 MHz, $CDCl_3$): 2.24–2.56 (m, 2H, $OCCH_2$–), 3.45–3.54 (m, 1H, H-2), 3.97–4.16 (m, 2H, OCH_2–), 5.05 (d, $J_{H3–H2} = 2.0$, 1H, H-3), 7.45 (s, 1H, OH). δ_C (50 MHz, $CDCl_3$): 28.8 ($OCCH_2$–), 49.0 (C-2), 68.1 (C-3), 69.0 (OCH_2–), 117.9 (CN), 174.1 (CO). GC–MS (EI, 70 eV) *m*/*z* (%): 141 (M^+, 1), 113 (28), 96 (76), 86 (97), 68 (100). IR (neat) 2500–3500, 2249, 1718.
Compound **2d** (major compound): δ_H (200 MHz, $CDCl_3$): 1.64–1.94 (m, 2H, $OCCCH_2$–), 2.06–2.27 (m, 2H, $OCCH_2$–), 2.78–2.94 (m, 1H, H-2), 3.64–4.11 (m, 2H, OCH_2–), 5.10 (d, 1H, $J_{H3–H2} = 4.0$, H-3), 8.42 (s, 1H, OH). δ_C (50 MHz, $CDCl_3$): 18.7 ($OCCCH_2$–), 21.9 ($OCCH_2$–), 43.2 (C-2), 64.4 (OCH_2–), 65.5 (C-3), 115.6 (CN), 173.7 (CO). GC–MS (EI, 70 eV) *m*/*z* (%): 155 (M^+, 1), 127 (28), 99 (51), 82 (67), 55 (100). IR (neat) 2500–3500, 2256, 1713.
Compound **2e**: δ_H (200 MHz, $CDCl_3$): 1.18 (d, 3H, $J = 6.0$, $OCCH_3$), 1.26 (d, 3H, $J = 6.2$, $OCCH_3$), 2.90 (d, 2H, $J_{H2–H3} = 6.6$, H-2), 3.91 (sep, 1H, $J = 6.0$, OCH–),4.62 (t, 1H, $J_{H3–H2} = 6.6$, H-3), 9.31 (s, 1H, OH). δ_C (100 MHz, $CDCl_3$): 20.7 ($OCCH_3$), 22. 5 ($OCCH_3$), 38.7 (C-2), 62.0 (OCH–), 73.1 (C-3), 117.9 (CN), 173.5 (CO). GC–MS (EI, 70 eV) *m*/*z* (%): 157 (M^+, 1), 142 (55), 115 (20), 98 (88), 80 (28), 54 (100). IR (neat) 2500–3500, 2254, 1719.
Compound **2f** (major compound): δ_H (200 MHz, $CDCl_3$): 1.16 (d, 3H, $J = 6.2$, CH_3), 1.26 (d, 3H, $J = 6.2$, $OCCH_3$), 1.38 (d, 3H, $J = 7.2$, $OCCH_3$), 2.90 (qui, 1H, $J = 7.6$, H-2), 3.89 (sep, 1H, $J = 6.2$, OCH–), 4.47 (d, 1H, $J_{H3–H2} = 8.2$, H-3), 9.94 (s, 1H, OH). δ_C (100 MHz, $CDCl_3$): 12.9 (–CCH_3), 20.7 ($OCCH_3$), 22.3 ($OCCH_3$), 43.5 (C-2), 68.0 (OCH–), 73.2 (C-3), 117.4 (CN), 177.3 (CO). GC–MS (EI, 70 eV) *m*/*z* (%): 144 (M^+−27, 2), 100 (13), 84 (14), 58 (100). IR (neat) 2500–3500, 2250, 1717.
Compound **2g** (major compound): δ_H (200 MHz, $CDCl_3$): 0.83–0.98 (m, 3H, –CH_3), 1.15 (d, 3H, $J = 5.8$, –CH_3), 1.38–1.66 (m, 2H, –CH_2CH_3), 2.9 (d, 2H, $J_{H2–H3} = 7.0$, H-2), 3.66 (sex, 1H, $J = 5.8$, OCH–), 4.56–4.68 (m, 1H, H-3), 9.76 (s, 1H, OH). δ_C (100 MHz, $CDCl_3$): 9.6 (–CH_3), 18.0 (–CH_3), 29.4 (–CH_2CH_3), 38.6 (C-2), 62.1 (O*CH*–), 77.7 (C-3), 117.8 (CN), 173.7 (CO). GC–MS (EI, 70 eV) *m*/*z* (%): 170 (M^+−H, 1), 142 (89), 115 (10), 98 (77), 80 (24), 54 (100). IR (neat) 2500–3500, 2252, 1720.
Compound **4**: Yield 40%, mp 138.5–141.5 °C. δ_H (400 MHz, DMSO): 1.25 (t, 3H, $J_{CH3–CH2} = 8.0$, CH_3), 3.72 (q, 2H, $J_{CH2–CH3} = 8.0$, OCH_2), 5.22 (s, 1H, CH), 7.20 (s, 1H, NH), δ_C (100 MHz, DMSO): 14.0 (CH_3), 63.2 (OCH_2), 103.5 (CH), 158.1 (C), 163.5 (CO), 167.3 (CO). GC–MS (EI, 70 eV) *m*/*z* (%): 142 (M^+, 6), 98 (9), 69 (100). IR (KBr) 3414, 1604.
Compound **5**: Yield 36%, mp 75–78 °C. δ_H (200 MHz, $CDCl_3$): 1.23 (t, 6H, $J = 8.0$, CH_3 e CH_3'), 2.9 (s, 2H, CH_2), 3.7 (q, 4H, $J = 8.0$, OCH_2, OCH_2'), 9.0 (s, 1H, NH). δ_C (100 MHz, $CDCl_3$): 14.9 ($2CH_3$), 41.7 (CH_2),59.2 ($2OCH_2$), 99.1 (C), 172.3 (CO), 173.0 (CO). GC–MS (EI, 70 eV) *m*/*z* (%): 187 (M^+, 1), 143 (13), 116 (100), 89 (39), 60 (65). Anal. Calcd for $C_6H_7NO_2$ (187): C, 51.33; H, 7.00; N, 7.48. Found: C, 51.28; H, 7.30; N, 7.41.
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